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Are liver abnormalities associated with hospital mortality in viral infections?

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Abstract

Objective: Patients hospitalised with severe viral infections may have abnormal liver function. Multiple studies have linked systemic-disseminated viral infections to liver damage. The progression, medical significance, and impact of atypical liver chemical levels on hospitalised infections are unknown.

Aims: This study addresses these concerns and examines how liver-related biochemical abnormalities affect viral infection patients' clinical outcomes.

Methods: A retrospective study was conducted at the royal medical services' institutions, focusing on patients admitted over two years. The primary purpose was to gather information about patients who underwent testing. Patients with abnormalities in liver indices, specifically alanine transferase (ALT) and aspartate aminotransferase (AST), were included in the study. Patients with an AST/ALT ratio greater than 2 were excluded. Patients were classified as either having a lower liver disease status (Status I) or a higher liver disease status (Status II). The classification of liver disease statuses was based on the LDH to AST ratio (below 6.5 or higher than 6.5). The study used independent T-tests, Chi Square Test, and multiple logistic regression to analyze non-parametric data. A significance level of 5% was chosen, and SPSS ver 25 was used for the study. The study aimed to determine the effects of gender, severity group at admission, and composite predictors on the likelihood of admitted viral infected patients having liver diseases.

Results: MAOVA analysis revealed a significant difference in overall mortality among individuals infected with SARS-VIRAL, based on the LDH: AST 1 and LDH: AST 2 ratios. The statistical test yielded an F-value of 1204.283 with degrees of freedom (2, 778), and a p-value of less than .0005. Additionally, Wilk's Lambda was found to be 0.244, indicating a strong effect size (partial $\eta 2 = 0.756$).

Conclusion: The involvement of the liver in viral infections is directly correlated with mortality, as this correlation is very clear. Therefore, it is of the utmost importance to incorporate hepatic enzymes as a criterion when evaluating patients who have viral infections. This is because of the impact that elevated liver enzymes have on immune cells and, as a result, the overall clinical outcomes. Since this is the case, it is essential for viral patients to undergo daily monitoring of their liver enzymes on a consistent basis.

Keywords: Liver abnormalities; Viral infections; Hospitalized patients; Child-Pugh score

1. Introduction

In hospitalised patients, systemic viral infections that cause a cytokine storm are frequently observed. This is especially true for patients who are elderly, those with compromised immune systems, and those who have multiple underlying health conditions. Take, for instance, the coronavirus-2019, which is a global pandemic disease that appeared in late

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2019 and spread rapidly, resulting in millions of deaths. It has affected over 200 countries and infected over 527,631,000 people, with 6,282,602 deaths as of the 25th of May in 2022. It is without a doubt that this infection that is associated with the coronavirus has resulted in a mortality rate of approximately 10% across the board 1-3.

The middle-east respiratory syndrome coronavirus, also known as MERS-CoV, is an additional example of a viral infection that is linked to systemic inflammatory response syndrome (SIRS) in admitted hospitalized patients. Seven hundred and seventy-nine deaths have been reported as a result of this virus, which has affected approximately 2182 people in 27 different countries. When compared to diseases caused by SARS-CoV-1 and MERS-CoV, diseases associated with SARS-CoV-2 have a greater capacity to cause disease, spread, and severity. As a result, they pose a greater threat to public health and mortality. The genome sequence of SARS-CoV-2, on the other hand, is approximately fifty percent similar to that of MERS-CoV and seventy-five percent similar to that of SARS-CoV-1. [4-5]

The respiratory symptoms are the primary manifestation of the majority of severe viral infections in patients who are infected. However, additional symptoms that are associated with a variety of organs, such as the cardiovascular system, the gastrointestinal system, the liver, the endocrine system, the haematological system, the renal system, the immunological system, and the dermatological system, may also be present. Infections caused by SARS-CoV-2, for example, are frequently accompanied by gastrointestinal symptoms that may become more severe over the course of the infection. These symptoms typically appear at an earlier stage. Patients with COVID-19 frequently report experiencing these symptoms, which include, but are not limited to, nausea, vomiting, diarrhoea, and abdominal cramping. [6-7]

In regards to viral infections linked to liver damage, all of the previously mentioned infections related to coronaviruses are commonly associated with liver diseases, with an occurrence rate ranging from 15% to 75%. In some cases, the symptoms of COVID-19 that affect the gastrointestinal tract may be the only signs present, leading to a delay in diagnosing the initial respiratory symptoms. The abundant presence of viral entry receptors, such as the ACE2 receptors in the case of SARS-CoV-2, within the gastrointestinal tract facilitates the cellular entry of viruses. However, the precise mechanisms through which the various viral pathogens contribute to the development of gut and liver diseases remain incompletely comprehended. [8-9]

A modest to moderate increase in transaminases and slightly elevated levels of bilirubin are observed in patients who have been admitted to the hospital with primary severe viral associated infections. This is a biochemical perspective. According to the severity of the disease, these elevated bilirubin levels are directly related to the symptoms. Lactate dehydrogenase (LDH), alanine transaminases (ALT), and aspartate transaminases (AST) are the three primary indices that are typically utilised in the process of evaluating the biochemical and clinical effects that viruses have on liver cells. There is a lack of sufficient clinical research on the LDH/AST ratio upon admission to forecast the progression of viral-induced cytokine storms in hospitalised patients. Although it is likely that elevated levels of AST and LDH in patients are associated with increased mortality, there is currently a dearth of such research. [10-11]

Patients who were admitted to our institutional department at the Royal Medical Services in Amman and who exhibited signs of a severe viral-related systemic inflammatory response syndrome are the subjects of this study, which presents a comprehensive analysis of the clinical outcomes, biochemical findings, sensitivity analysis, and prognostic logistic regression modelling.

2. Methods

This research was carried out in a retrospective manner. Within the Royal Medical Services, the study was subjected to evaluation, and it was granted approval by the standing committee that is responsible for coordinating health and medical research. The demographic, anthropometric, biochemical, and nutritional information of patients was collected on a retrospective basis from our electronic medical record system (Hakeem) for a period of approximately 2 years, beginning in January 2021 and ending in December 2022. Patients who were younger than 18 years old, had a length of stay (LOS) in the hospital that was longer than seven days, and had missing data for the variables that were being studied were not included in the study.

The requirement that a signed consent form be submitted was not necessary because our research was conducted in a retrospective manner. In the course of the research, every single patient who was eligible to participate displayed a spectrum of disease severity, ranging from moderate to severe. Patients who were critically ill and were being ventilated mechanically and who were severely affected by ARDS were included in this category. Patients who tested negative for PCR but exhibited clinical, biochemical, and radiological signs of invasive viral-associated cytokine storms were

classified as suspected viral infections. This was the case regardless of whether the patients were associated with severe influenza, SARS, or other viral infections that have not yet been identified.

Patients were considered to be confirmed cases of viral infection if they tested positive for SARS-CoV-2 through the test of polymerase chain reaction (PCR). The patients who participated in our study were those who had been confirmed to have a viral infection as well as those who were suspected of having a viral infection.

Through the use of mathematical calculations, the hemodynamic variables of Shock Index (SI) and modified Shock Index (mSI) were obtained. These variables were obtained by dividing the heart rate by the systolic blood pressure (SBP) and the mean arterial pressure, respectively, in a manner that was retrospective. On the basis of the primary retrievable data, the ratios of prognosticators were computed. These ratios included the c-reactive protein (CRP) to albumin ratio (CRP: ALB), the ferritin to albumin ratio (FER: ALB), the neutrophils to lymphocytes ratio (NLR), and the monocytes to lymphocytes ratio (MLR).

There were two categories of variables that could be obtained and calculated: parametric data and non-parametric data. Both of these categories were separated into two categories. The parametric data were compared between two groups: Cohort I, which consisted of SARS-CoV-2 infected patients with an LDH: AST 1 ratio that was significantly lower than 6.5:1, and Cohort II, which consisted of SARS-CoV-2 infected patients with an LDH: AST 1 ratio that was greater than or equal to 6.5:1. For the purpose of analysing the comparative parametric data, univariate tests were employed, and the outcomes were expressed as either Mean±standard deviation (SD) or Mean difference±standard error of the mean (SEM). In order to investigate the data, the Chi Square Test was utilised to conduct an analysis of the non-parametric variables. The outcomes were expressed as numbers (percentage), and the odds ratio (OD) was used to express the relative risk estimates. The results of the outcome were expressed as numbers. At Queen Alia Military Hospital in Jordan, between the months of March 2020 and September 2021, a comparison was made between two cohorts of SARS-CoV-2 infected patients. The variables of the patients were compared. Cohort I was comprised of patients who had low-density lipoprotein (LDH) and an AST level of less than 6.5, while Cohort II was comprised of patients who had an AST level of greater than or equal to 6.5. Tables 1 through 3 contain a summary of the findings that were obtained.

The Multiple Logistic Regression Test was carried out in order to investigate the extent of the associations, the percentage of the total variations in the dependent variable that can be accounted for by the independent variables, and the degree of accuracy with which the dependent variable could be predicted. For the purpose of determining the impact of gender, severity group at admission, and the primary predictor, %Δ FER: ALB to LMR 12, on the probability of SARS-CoV-2 infected patients with liver diseases, as indicated by LDH: AST 1 ≥6.5, the study employed the Multiple Logistic Regression Test analysis. The purpose of this test was to determine the essential coefficients that are necessary for predicting the diagnosis of liver disease in patients who were infected with SARS-CoV-2. Additionally, the purpose of this event was to present the final version of the Multiple Logistic Regression model that we had proposed for patients who were afflicted with viral infections.

The Ratio-Occurrence (ROC) analysis was conducted in order to evaluate the correlation between the area under the curve and the total number of SARS-CoV-2 infected patients who were diagnosed with liver diseases. These patients were classified according to their LDH: AST 1 values, with a value of 6.5 or higher. There were 781 cases in the dataset that was used for the sensitivity analysis that was carried out. There were 155 cases that were classified as having a positive actual state, while there were 626 cases that were classified as having a negative actual state. There were no cases that were analysed and considered to be missing data. The more significant the values of the test result variable(s), the more convincing the evidence is that the actual state is going to be positive. The current situation pertains to patients who have been diagnosed with SARS-CoV-2 and also have liver diseases, as indicated by a ratio of LDH to AST 1 that is equal to or greater than 6.5.

The purpose of this study was to determine the thresholds, sensitivities, specificities, positive and negative predictive values, Youden and accuracy indices, and negative likelihood ratios for LDH: AST 1 and LDH: AST 2 that were the most effective in predicting the presence of liver diseases in SARS-CoV-2 infected patients who were admitted to the hospital. The presence of liver diseases was found to be indicated by the presence of LDH: AST 1 ≥6.5.

In conclusion, the one-way multivariate analysis of variance (one-way MANOVA) was utilised in order to determine whether or not there are any differences between the independent groups with regard to the multiple continuous dependent variables.

3. Results

From January 2021 to December 2022, a total of 718 adult inpatients at King Hussein Medical Centre in Amman, Jordan were included in this study. Among them, 247 patients (31.6%) were suspected to have a viral infection, while 534 patients (68.4%) were confirmed to have an infection. The average age of all patients in the study was 59.40±10.60 years. Non-survivors had a higher average age compared to survivors, with survivors being younger at 58.35±10.20 years and non-survivors at 59.66±10.69 years. The p-value for this difference is 0.17. Based on gender, males were distributed in a ratio of approximately 2.31 to 1 compared to females, with 545 males (69.8%) and 236 females (30.2%) respectively. The p-value for this distribution is 0.829. In the study, 67.7% of the male participants (105 patients) were affected, while 32.3% of the female participants (50 patients) who were affected belonged to the non-survivors' group. In contrast, 70.3% of the affected male participants (440 patients) and 29.7% of the affected female participants (186 patients) belonged to the survivors' group. All of this data is presented in Table 1.

Table 1 Comparatively studied variables between viral infected patients whose LDH: AST_1 was <6.5: 1 Cohort (Cohort I) and viral infected patients whose LDH: AST_1 was ≥6.5: 1 Cohort (Cohort II)

Studied Comparative Variables		**Overall Cohorts (N=781) Mean±SD**	**Cohort I (N= 392, 50.19%) Mean±SD**	**Cohort I (N=389, 49.81%) Mean±SD**	**Mean Diff±SEM or OD**	**P-Value**
Gender	F	236 (30.2%)	151 (38.5%)	85 (21.9%)	2.24 (95% CI; 1.64-3.07)	0.000
	M	545 (69.8%)	241 (61.5%)	304 (78.1%)		
	M: F ratio	2.31: 1	1.6: 1	3.58: 1		
VIRAL case	Suspected	247 (31.6%)	119 (30.4%)	128 (32.9%)	0.89 (95% CI; 0.66-1.20)	0.444
	Confirmed	534 (68.4%)	273 (69.6%)	261 (67.1%)		
FCR_1		12.48±1.12	12.52±0.50	12.43±1.50	0.08±0.08	0.312
FCR_2		14.41±3.46	13.44±0.93	15.38±4.62	-1.94±0.24	0.000
FER_1		746.5±310.7	714.0±194.5	779.3±392.1	-65.3±22.1	0.003
ALB_1 (g/dl)		2.21±0.38	2.23±0.35	2.18±0.40	0.06±0.03	0.033
FER: ALB_1		362.1±206.2	337.27±123.72	387.14±262.26	-49.87±14.66	0.001
CRP_1 (mg/dl)		59.65±22.74	56.91±15.06	62.41±28.21	-5.49±1.62	0.001
CRP: ALB_1		28.83±15.11	26.83±9.58	30.85±18.92	-4.02±1.07	0.000
FER_2 (ng/ml)		855.1±503.0	769.4±333.7	941.5±617.8	-172.0±35.5	0.000
ALB_2 (g/dl)		3.19±0.64	3.19±0.57	3.18±0.71	0.02±0.05	0.729
FER: ALB_2		298.9±233.0	261.23±139.83	336.81±294.13	-75.58±16.46	0.000
CRP_2 (mg/dl)		56.88±24.55	56.54±23.49	57.21±25.60	-0.67±1.76	0.704
CRP: ALB_2		19.62±11.46	19.15±9.93	20.09±12.82	-0.94±0.82	0.250
%ΔFER: ALB_{12}		-23.9%±28.1%	-27.5%±20.0%	-20.2%±33.9%	-7.2%±2.0%	0.000
%ΔCRP: ALB_{12}		-34.7%±18.0%	-32.6%±18.0%	-36.8%±17.8%	4.1%±1.3%	0.001
%ΔFCR_{12}		14.2%±17.8%	7.3%±4.5%	21.2%±22.8%	-13.9%±1.2%	0.000
The Non-categorical data results of the comparative variables between the Cohort I and Cohort II were statistically analyzed by Univariate comparative tests (at p-value< 0.05) and expressed as Mean±SD and Mean difference±SEM. While the categorical data results of the comparative variables between the 2 tested cohorts were statistically						

analyzed by Chi Square Test (at p-value< 0.05) and expressed as Number (Percentage). Also, the Chi Square Test was used to explore the association strength between the dichotomous comparative tested variables. Cohort I: Admitted viral infected patients whose LDH: AST $_1$ was <6.5: 1. Cohort II: Admitted viral infected patients whose LDH: AST $_1$ was ≥6.5: 1	
FCR_1: Baseline ferritin to c-reactive protein ratio. FCR_2: Ferritin to c-reactive protein ratios average during admission. FER: ALB_1: Baseline ferritin to albumin ratio. FER: ALB_2: Ferritin to albumin ratios average during admission. CRP: ALB_1: Baseline c-reactive protein to albumin ratio. CRP: ALB_2: C-reactive protein to albumin ratios average during admission. %ΔFER: ALB_{12}: Percentage changes of ferritin to albumin ratios. %ΔCRP: ALB_{12}: Percentage changes of c-reactive protein to albumin ratios. %ΔFCR_{12}: Percentage changes of ferritin to c-reactive protein ratios. %TLC_{12}: Percentage changes of total lymphocyte counts.	FER_1: Baseline ferritin level. ALB_1: Baseline albumin level. CRP_1: Baseline c-reactive protein level. FER_2: Ferritin levels average during admission. ALB_2: Albumin levels average during admission. CRP_2: C-reactive protein levels average during admission. F: Female. M: Male. M: F: Male to Female ratio. Significant: (P-Value <0.05).

The distribution of oxygen supply strategies differed significantly between the Survivors Cohort (Cohort I) and Non-Survivors Cohort (Cohort II). In Cohort I, 76 individuals (9.7%) were not receiving oxygen, 332 individuals (42.5%) were using nasal cannula at a flow rate of 3-6 L/min, 357 individuals (45.7%) were on non-invasive mechanical ventilation, and 16 individuals (2.0%) were on invasive mechanical ventilation. In contrast, in Cohort II, 76 individuals (20.2%) were not receiving oxygen, 205 individuals (54.5%) were using nasal cannula at a flow rate of 3-6 L/min, 95 individuals (25.3%) were on non-invasive mechanical ventilation, and none were on invasive mechanical ventilation. The Survivors Cohort had a lower average intake of human albumin compared to the Non-Survivors Cohort (12±4 g/day vs 18±4 g/day, a difference of -7±0 g/day, p-value=0.00). However, there were no significant changes in serum albumin levels between the two cohorts (%ΔALB 12: 44.8%±12.9% vs 44.5%±34.8%, a difference of 0.3%±1.7%, p-value=0.843). The Non-Survivors Cohort had a significantly higher average Paracetamol dose compared to the Survivors Cohort [3.32±0.46 g/day vs 1.55±0.65 g/day, +1.77±0.06, p-value=0.00]. Additionally, the percentage distribution of Paracetamol administered intravenously (IV) compared to orally (P.O) was significantly higher in the Non-Survivors Cohort [151 (97.4%) vs 132 (21.1%)] compared to the Survivors Cohort [4 (2.6%) vs 494 (78.9%)]. The allocation of antibiotics differed insignificantly between the two cohorts under study. Specifically, in the Survivors Cohort, 51.6% received non-Tazocin® antibiotics and 48.4% received Tazocin® antibiotics, while in the Non-Survivors Cohort, 51.6% received non-Tazocin® antibiotics and 48.4% received Tazocin® antibiotics. Based on estimated creatinine clearance (CrCl) using the Jelliffe equation, the Survivors Cohort had a significantly lower percentage deficit in prescribing PIP/TAZ (Tazocin®) and IMI/CIL (Imipenem®) compared to the Non-Survivors Cohort (-27.73%±3.92% and -28.73%±5.85% vs -30.21%±4.06% and -38.67%±8.13%, respectively, p-Value=0.00). The average corrected sodium level (cNa2) was significantly higher in the Survivors Cohort compared to the Non-Survivors Cohort [137.86±3.16 mEq/l vs 128.77±3.84 mEq/l, a difference of +9.09±0.30mEq/l, p-value=0.00]. Additionally, the incidence of hyponatremia was significantly higher in the Non-Survivors Cohort compared to the Survivors Cohort [155 (100.0%) vs 471 (75.2%), respectively, p-value=0.00]. The average blood glucose levels (BG2) in the survivor's cohort were slightly higher than those in the non-survivor's cohort [153.04±39.18 mg/dl vs 147.74±20.81 mg/dl; +5.30±3.26 mg/dl, p-Value=0.10], but the difference was not statistically significant. In contrast, the Survivors Cohort had a significantly lower average total daily insulin dose compared to the Non-Survivors Cohort [31.74±1.80 IU/day vs 33.55±1.90 IU/day; -1.82±0.16 IU/day, p-Value=0.00], as shown in Table 2.

Table 2 Comparatively studied variables between viral infected patients whose LDH: AST 1 was <6.5: 1 Cohort (Cohort I) and viral infected patients whose LDH: AST 1 was ≥6.5: 1 Cohort (Cohort II)

Studied Comparative Variables		**Overall Cohorts (N=781) Mean±SD**	**Cohort I (N= 392, 50.19%) Mean±SD**	**Cohort I (N=389, 49.81%) Mean±SD**	**Mean Diff±SEM or OD**	**P-Value**
VIRAL severity	Mild-Moderate	393 (50.3%)	190 (48.5%)	203 (52.2%)	0.86 (95% CI; 0.65-1.14)	0.299
	Severe-Critical	388 (49.7%)	202 (51.5%)	186 (47.8%)		
Dex	None	376 (48.1%)	179 (45.7%)	197 (50.6%)	0.82 (95% CI; 0.62-1.09)	0.164
	Yes	405 (51.9%)	213 (54.3%)	192 (49.4%)		
O2 supply	None	177 (22.7%)	109 (27.8%)	68 (17.5%)	NA	0.000
	NC (3-6 L/min)	223 (28.6%)	96 (24.5%)	127 (32.6%)		
	NIMV	203 (26.0%)	116 (29.6%)	87 (22.4%)		
	IMV	178 (22.8%)	71 (18.1%)	107 (27.5%)		
HALB (g/day)		81.8±38.1	74.84±25.24	88.73±46.66	-13.89±2.68	0.000
HLOS (days)		11.6±1.6	11.33±1.13	11.88±1.91	-0.55±0.11	0.000
Age (age)		59.4±10.6	59.68±10.62	59.12±10.60	0.57±0.76	0.457
BW (Kg)		73.7±10.0	73.28±9.73	74.18±10.30	-0.90±0.72	0.209
BMI (Kg/m^2)		25.95±3.89	26.08±3.95	25.81±3.83	0.27±0.28	0.325
$Tavg_1$ (◦ C)		37.64±0.95	37.43±0.81	37.86±1.03	-0.43±0.07	0.000
$Tavg_2$ (◦ C)		36.86±1.26	36.67±0.50	37.04±1.70	-0.37±0.09	0.000
Insulin IU/hr		1.34±0.09	1.34±0.09	1.33±0.08	0.01±0.01	0.385
$\%WBC_{12}$		14.7%±24.6%	18.5%±25.4%	10.9%±23.0%	7.6%±1.7%	0.000
$\%MLR_{12}$		-69.6%±27.4%	-76.1%±12.1%	-63.0%±35.7%	-13.1%±1.9%	0.000
%ΔFER: ALB to LMR_{12}		-72.2%±33.8%	-82.7%±9.5%	-61.6%±44.5%	-21.0%±2.3%	0.000
%ΔCRP: ALB to LMR_{12}		-76.0%±32.0%	-71.0%±42.4%	-81.0%±14.0%	10.0%±2.3%	0.000
$\%\Delta BUNSCr_{12}$		-32.8%±15.8%	-36.3%±17.3%	-29.2%±13.1%	-7.2%±1.1%	0.000
CrCl_ Jelliffe eq		48.56±5.45	49.73±1.65	47.37±7.36	2.36±0.38	0.000

The Non-categorical data results of the comparative variables between the Cohort I and Cohort II were statistically analyzed by Univariate comparative tests (at p-value< 0.05) and expressed as Mean±SD and Mean difference±SEM. While the categorical data results of the comparative variables between the 2 tested cohorts were statistically analyzed by Chi Square Test (at p-value< 0.05) and expressed as Number (Percentage). Also, the Chi Square Test was used to explore the association strength between the dichotomous comparative tested variables.

Cohort I: Admitted viral infected patients whose LDH: AST 1 was <6.5: 1.

Cohort II: Admitted viral infected patients whose LDH: AST 1 was ≥6.5: 1

$\%WBC_{12}$: Percentage changes of white blood cells.	BMI: Body mass index in Kg per m^2.
$\%TLC_{12}$: Percentage changes of total lymphocyte counts.	

$\%MC_{12}$: Percentage changes of monocyte counts. $\%MLR_{12}$: Percentage changes of monocyte to lymphocyte ratios. %ΔFER: ALB to LMR_{12}: Percentage changes of FER: ALB to reverse MLR. %ΔCRP: ALB to LMR_{12}: Percentage changes of CRP: ALB to reverse MLR. $\%\Delta BUNSCr_{12}$: Percentage changes of BUN to SCr. NC: Nasal canula on oxygen flow rate of 3-6 L/min. NIMV: Non-invasive mechanical ventilation. IMV: Invasive mechanical ventilation.	T_{avg1}: Baseline average core body temperatures in ° C. T_{avg2}: Average Core body temperatures in ° C. Insulin $_{rate}$: Insulin infusion rate in IU/hr. HALB: Human albumin 20% inputs average in g/day. HLOS: Hospital length of stay days. $CrCl_{\_\ Jelliffe\ eq}$: Creatinine clearance based on Jelliffe eq. Dex: Dexamethasone. NA: Not statistically applicable and can't be computed. N: Number of tested VIRAL patients.

In terms of hemodynamics, the Survivors Cohort experienced a much greater decrease in SI and mSI (%ΔSI and %ΔmSI, respectively) compared to the Non-Survivors Cohort [-25.3%±11.8% and -31.2%±11.3% vs -0.9%±6.0% and -7.5%±6.0%, respectively, p-value=0.00]. The bilirubin levels and INR of SARS-CoV-2 infected patients in the Non-Survivors Cohort were significantly higher compared to those in the Survivors Cohort [2.71±0.16 mg/dl and 2.68±0.11 vs 2.53±0.18 mg/dl and 2.57±0.11, respectively, p-value=0.00]. The Survivors Cohort had significantly lower total calorie intake (523.2±192.7 Cal/day) and protein density (1.92±1.03 g/100 Cal) compared to the Non-Survivors Cohort (766.9±208.0 Cal/day and 2.56±0.73 Cal, respectively, p-value=0.00). Additionally, carbohydrate density was significantly higher in the Survivors Cohort (20.62±4.70 g/100 Cal) compared to the Non-Survivors Cohort (17.71±3.39 g/100 Cal; 2.91±0.40 g/100 Cal, p-Value=0.00). The reduction percentages in various blood cell counts and ratios were significantly higher in the Survivors Cohort compared to the Non-Survivors Cohort. Specifically, there were significant reductions in white blood cell counts (-26.9%±28.7%), absolute neutrophil counts (-41.4%±30.6%), monocyte counts (51.7%±37.3%), neutrophil to lymphocyte ratios (-48.0%±15.2%), and monocyte to lymphocyte ratios (-58.3%±12.8%). In contrast, the Non-Survivors Cohort showed increases in these measures, with white blood cell counts increasing by +36.0%±15.8%, absolute neutrophil counts by +22.9%±14.7%, monocyte counts by +27.1%±18.0%, neutrophil to lymphocyte ratios by +23.7%±146.0%, and monocyte to lymphocyte ratios decreasing by -6.9%±103.3%. The p-value for these differences was 0.000. The reduction percentages in the ratios of FER: ALB and CRP: ALB (%ΔFER: ALB 12 and %ΔCRP: ALB 12 , respectively) were significantly higher in the Survivors Cohort compared to the Non-Survivors Cohort [-62.9%±13.0% and -63.7%±12.7% vs -39.1%±8.1% and -41.8%±8.3%, respectively, p-value=0.00]. In our study, we examined the overall mortality and overall survival rates (N=155, 19.85% and N=626, 80.15% respectively). Additionally, we analysed the overall hospital length of stay (LOS) and found that it was significantly shorter in the Non-Survivors Cohort compared to the Survivor Cohort (10.45±2.08 days vs 11.42±2.98 days, p-Value=0.00). The two studied cohorts showed negligible disparities in their baseline anthropometric measurements, as presented in Table 3.

Table 3 Comparatively studied variables between viral infected patients whose LDH: AST_1 was <6.5: 1 Cohort (Cohort I) and viral infected patients whose LDH: AST_1 was ≥6.5: 1 Cohort (Cohort II)

Studied Comparative Variables	**Overall Cohorts (N=781) Mean±SD**	**Cohort I (N= 392, 50.19%) Mean±SD**	**Cohort I (N=389, 49.81%) Mean±SD**	**Mean Diff±SEM or OD**	**P-Value**
Bil_1 (mg/dl)	1.30±0.89	1.22±0.36	1.38±1.20	-0.15±0.06	0.016
Bil_2 (mg/dl)	1.74±1.07	1.62±0.41	1.87±1.44	-0.25±0.08	0.001
ALT_1 (IU/L)	32.63±16.85	30.04±5.95	35.25±22.83	-5.20±1.19	0.000
ALT_2 (IU/L)	35.40±21.46	31.70±7.18	39.13±29.09	-7.42±1.51	0.000
AST_1 (IU/L)	38.27±13.24	37.31±4.91	39.23±18.07	-1.91±0.95	0.043
AST: ALT_1	1.29±0.24	1.26±0.09	1.32±0.33	-0.07±0.02	0.000
AST_2 (IU/L)	43.94±17.52	41.92±6.04	45.98±23.92	-4.07±1.25	0.001

AST: ALT $_2$	1.45±0.40	1.35±0.12	1.56±0.54	-0.21±0.03	0.000
LDH $_1$ (IU/L)	253.91±97.42	232.19±40.43	275.80±128.35	-43.61±6.80	0.000
LDH: AST $_1$	6.60±0.46	6.19±0.27	7.01±0.05	-0.82±0.01	0.000
LDH $_2$ (IU/L)	265.26±105.99	241.40±42.65	289.31±139.98	-47.91±7.39	0.000
LDH: AST $_2$	6.09±0.45	5.73±0.21	6.44±0.32	-0.71±0.02	0.000
PT $_1$ (seconds)	11.51±1.27	11.40±0.84	11.62±1.58	-0.22±0.09	0.015
PT $_2$ (seconds)	12.82±1.81	12.56±0.98	13.07±2.34	-0.51±0.13	0.000
aPTT $_1$ (seconds)	32.20±5.30	32.06±2.91	32.33±6.92	-0.27±0.38	0.476
aPTT $_2$ (seconds)	35.64±6.35	35.21±3.17	36.08±8.40	-0.87±0.45	0.054

The Non-categorical data results of the comparative variables between the Cohort I and Cohort II were statistically analyzed by Univariate comparative tests (at p-value< 0.05) and expressed as Mean±SD and Mean difference±SEM. While the categorical data results of the comparative variables between the 2 tested cohorts were statistically analyzed by Chi Square Test (at p-value< 0.05) and expressed as Number (Percentage). Also, the Chi Square Test was used to explore the association strength between the dichotomous comparative tested variables.

Cohort I: Admitted viral infected patients whose LDH: AST 1 was <6.5: 1.

Cohort II: Admitted viral infected patients whose LDH: AST 1 was ≥6.5: 1

Bil $_1$: Baseline bilirubin level levels in mg per dl.

Bil $_2$: Bilirubin levels averages during admission in mg/dl.

ALT $_1$: Baseline Alanine aminotransferase levels in IU per L.

ALT $_2$: Alanine transferase levels average during admission in IU per L.

AST $_1$: Baseline aspartate aminotransferase levels in IU per L.

AST: ALT $_1$: Baseline AST to ALT ratio.

AST $_2$: Aspartate aminotransferase levels average in IU per L.

AST: ALT $_2$: AST to ALT ratios average during admission.

LDH $_1$: Baseline Lactate dehydrogenase level in IU/L.

LDH: AST $_1$: Baseline LDH to AST ratio.

LDH $_2$: Lactate dehydrogenase levels average in IU/L.

LDH: AST $_2$: LDH to AST ratios average while admission.

PT $_1$: Baseline prothrombin time in seconds.

PT $_2$: Prothrombin times average while admission in seconds.

aPTT $_1$: Baseline activated partial thromboplastin time.

aPTT $_2$: Activated partial thromboplastin times average.

Table 4 Multiple Logistic Regression results for the 5 tested variables regarding viral infected patients' liver diseases risk as illustrated by elevation LDH: AST $_1$ above 6.5

Tested predictors	**B±SEM**	**Wald**	**df**	**Sig.**	**Exp(B)**	**95% C.I.for EXP(B)**	
						Lower	**Upper**
Gender	0.756±0.186	16.442	1	0.000	2.130	1.478	3.069
Age (Yrs)	-0.011±0.008	1.903	1	0.168	0.989	0.974	1.005
BMI (Kg/m^2)	-0.003±0.021	0.023	1	0.879	0.997	0.956	1.039
Severity Group	-1.8660.227	67.480	1	0.000	0.155	0.099	0.241
%Δ FER: ALB to LMR 12	0.057±0.006	92.582	1	0.000	1.059	1.047	1.071
Constant	5.425±0.953	32.421	1	0.000	226.990		

The Multivariate Logistic Regression Test was conducted to explore the degree of correlations, how much of the total variations in the dependent variable can be explained by the independent variables, and the quality of the prediction of the dependent variable.

The logistic regression model was statistically significant, $\chi 2(8) = 146.822$, $p < .0005$. The explained variation in the dependent variable based on our model ranges from 22.3% to 29.7%, depending on whether you reference the Cox & Snell R2 or Nagelkerke R2 methods, respectively, and correctly classified 67.1% of cases.

The Multivariate Logistic Regression Test was performed to ascertain the effects of gender, severity group at admission, and the primary our tested composite predictor, %Δ FER: ALB to LMR $_{12}$, on the likelihood that admitted SARS-CoV-2 infected patients have liver diseases as signified by LDH: AST 1 ≥6.5. Also, this test was conducted to abstract the necessary coefficients to collectively predict viral infected patients liver diseases status and to present the final form of our proposed multivariate logistic regression model for the affected VIRAL patients which can be formulated as follows.

likelihood that admitted viral infected patients have liver diseases as signified by LDH: AST 1 ≥6.5

$$= e^{(5.425+0.756\times\text{Gender}+0.057\times\%\Delta\text{FERALB: LMR 12}-1866.23\times\text{Severity Group})} / (1+ e^{(5.425+0.756\times\text{Gender}+0.057\times\%\Delta\text{FERALB: LMR 12}-1866.23\times\text{Severity Group})})$$

Cohort I: Admitted viral infected patients whose LDH: AST 1 was <6.5: 1.

Cohort II: Admitted viral infected patients whose LDH: AST 1 was ≥6.5: 1

%Δ FER: ALB to LMR $_{12}$: Percentage changes of Ferritin: Albumin to Lymphocytes: Monocyte's ratio from baseline admission level.

Severity Group: viral infected patients' severities on admission which categorized into either Mild/Moderate or Severe/Critical.

Table 5 The optimal cut-off points, sensitivities, specificities, positive and negative predictive values, Youden and accuracy indices, and the negative likelihood ratios for LDH: AST $_1$ and LDH: AST $_2$ in prognosticating the likelihood that admitted viral infected patients have liver diseases as signified by LDH: AST 1 ≥6.5

Prognostic Indicator	**Cutoff**	**TPR**	**FPR**	**YI**	**TNR**	**PPV**	**NPV**	**NLR**	**AI**
LDH: AST $_1$	7.0050	98.7%	7.8%	90.88%	92.17%	75.74%	99.65%	1.40%	93.47%
LDH: AST $_2$	5.9750	91.0%	45.0%	45.92%	54.95%	33.33%	96.09%	16.44%	62.10%

The area under the receiver operating characteristic (ROC) analysis was constructed against the overall admitted viral infected patients who have liver diseases as signified by LDH: AST $_1$ ≥6.5 (1) vs LDH: AST $_1$<6.5 (0). Sensitivity analysis was processed on a total of 781 processed cases, 155-case were processed as positive actual state, and 626-case were processed as a negative actual state. 0 processed cases were dealt with as missing data. higher values of the test result variable(s) indicate stronger evidence for a positive actual state. The positive actual state is the admitted viral infected patients who have liver diseases as signified by LDH: AST $_1$ ≥6.5.

LDH: AST $_1$: Admission lactate dehydrogenase to aspartate aminotransferase ratio.

LDH: AST $_2$: Lactate dehydrogenase to aspartate aminotransferase ratios average during admission days.

TPR: True positive rate (sensitivity).

FPR: False positive rate.

YI: Youden index.

TNR: True negative ratio (specificity).

PPV: Positive predictive value.

NPV: Negative predictive value.

NLR: Negative likelihood ratio.

AI: Accuracy index.

MAOVA analysis revealed a significant difference in overall mortality among individuals infected with SARS-VIRAL, based on the LDH: AST 1 and LDH: AST 2 ratios. The statistical test yielded an F-value of 1204.283 with degrees of freedom (2, 778), and a p-value of less than .0005. Additionally, Wilk's Lambda was found to be 0.244, indicating a strong effect size (partial $\eta 2 = 0.756$).

4. Discussion

The current study looked at information that was stored in the database of the King Hussein Medical Centre. Both cohort 2 (consisting of patients who did not survive) and cohort 1 (consisting of patients who did survive) were considered to be patients in the critical care unit. The time period covered by the study was from January 2021 to December 2022. The comprehensive analysis of a wide range of comparative variables, including anthropometrical, biochemical, hemodynamical, haematological, and prognosticate tested variables, is what makes our research stand out from others in the field. In addition, we have investigated the prognosticator of liver index ratio (LDH: AST) in both the cohorts of survivors and their counterparts who did not survive the disease. [12-13]

Several studies, including meta-analyses and systematic reviews, have been conducted to investigate the risk factors that are associated with unfavourable clinical outcomes in individuals who have been affected by viral infections. However, at the time that these studies were being carried out, the vast majority of the patients who were contributing to them had not yet achieved the outcomes that were desired for the study. The relatively small sample sizes of these studies introduced bias, which rendered predictions regarding the progression of viral diseases and the mortality rates of infected patients unreliable. In addition, the studies' sample sizes were relatively small. [14-15]

It is a widely held belief that T cells are necessary for the elimination of invasive viral infections from infected cells. Some examples of these infections include MERS-CoV, SARS-CoV 1, and SARS-CoV 2. It has been demonstrated through observational studies that there is a significant inverse relationship between total lymphocyte counts (TLC) and overall clinical outcomes. A prolonged and severe decrease in lymphocyte count, along with an increase in white blood cell count, was linked to a higher likelihood of death, according to an analysis of 138 individuals who were admitted to hospitals in Wuhan, China, after being infected with SARS-CoV-2. Other factors that were evaluated included an increase in the number of white blood cells. [16-17]

According to what was mentioned earlier in this research, people who are infected with the virus are likely to have impaired immune responses in their white blood cells, particularly in their lymphocytes and macrophages. This dysfunction may be associated with a significantly higher occurrence of complications during hospitalisation as well as multiple organ failures in patients who have moderate to severe SARS-CoV-2 infection and high blood sugar levels that are not under control. This is consistent with previous research that has shown that elevated levels of liver transaminases and dehydrogenases are linked to a significant rise in the number of complications that are associated with viral-associated acute respiratory distress syndrome (ARDS) in patients who are severely infected. Furthermore, prolonged periods of liver enzyme levels that are not under control are a significant contributor to the development of other concurrent medical conditions. These conditions are primarily associated with the overall mortality rate of individuals who are affected by viral infections. [18-19]

In our research, we discovered that the Survivors Cohort had higher levels of liver enzymes on average than the Non-Survivors Cohort. This was the case when comparing the two groups. On the other hand, the difference in these levels, as measured by the standard error of the mean (±SEM), was clinically insignificant. However, we found that the average ratios of liver enzymes in the Survivors Cohort were significantly lower than those in the Non-Survivors Cohort. This was something that we observed. Despite the fact that the precise mechanisms that underlie the connection between hyper-transaminasemia and the severity and death rates of viral diseases are not yet completely understood, there is a growing body of evidence that suggests a connection between the two. Individuals who have hyper-transaminasemia may have a higher expression of viral entry receptors, such as ACE 2 in patients who are infected with SARS-CoV-2, according to the evidence presented here. They are more susceptible to the virus's ability to bind to them and enter their bodies as a result of this increased expression. When it comes to reducing the progression and fatality rate of viral patients, it can be beneficial to effectively track, monitor, and manage the levels and ratios of liver enzymes. The purpose of this study was to investigate the potential impact that liver-related prognosticators could have on the mortality rate of patients who were infected with a viral disease. Based on the findings, it appears that these prognosticators have the potential to be utilised for the purpose of early detection of the progression of viral disease with a high level of sensitivity, specificity, and accuracy. [20-21]

Considering that there is currently no specific treatment available for viral infections such as influenza and novel coronavirus, it is essential to determine whether or not the treatments that are being proposed are effective. Currently, the therapeutic approach involves the administration of medications that have the potential to cause harm to the liver. Some examples of these medications include oseltamivir, hydroxychloroquine, paracetamol, and acetaminophen. Because of this, it is of the utmost importance to carry out research on the connection between viral infections and the liver disease. Having this knowledge will make it possible for medical professionals to reduce the risk that their patients are exposed to and to prevent fatalities that are caused by liver damage caused by viral infections. [22]

Table 6 Comparatively studied variables between the 2 compared liver indices' ratios at and during admissions, [LDH to AST ratio] among admitted affected VIRAL patients

LDH: AST 1			**LDH: AST 2**		
Survivors (N=626) Mean±SD	**Non-Survivors (N=155) Mean±SD**	**Total (N=781) Mean±SD**	**Survivors (N=626) Mean±SD**	**Non-Survivors (N=155) Mean±SD**	**Total (N=781) Mean±SD**
6.487±0.445	7.047±0.0176	6.598±0.457	12.84±1.520	6.097±0.077	6.086±0.448

Effect		Value	F	Hypothesis df	Error df	Sig.	Partial Eta Squared
Intercept	Pillai's Trace	0.996	87917.571	2.000	778.000	0.000	0.996
	Wilks' Lambda	0.004	87917.571	2.000	778.000	0.000	0.996
	Hotelling's Trace	226.009	87917.571	2.000	778.000	0.000	0.996
	Roy's Largest Root	226.009	87917.571	2.000	778.000	0.000	0.996
Overall Mortality	Pillai's Trace	0.756	1204.283	2.000	778.000	0.000	0.756
	Wilks' Lambda	0.244	1204.283	2.000	778.000	0.000	0.756
	Hotelling's Trace	3.096	1204.283	2.000	778.000	0.000	0.756
	Roy's Largest Root	3.096	1204.283	2.000	778.000	0.000	0.756

The one-way multivariate analysis of variance (one-way MANOVA) is used to determine whether there are any differences between independent groups on more than one continuous dependent variable.

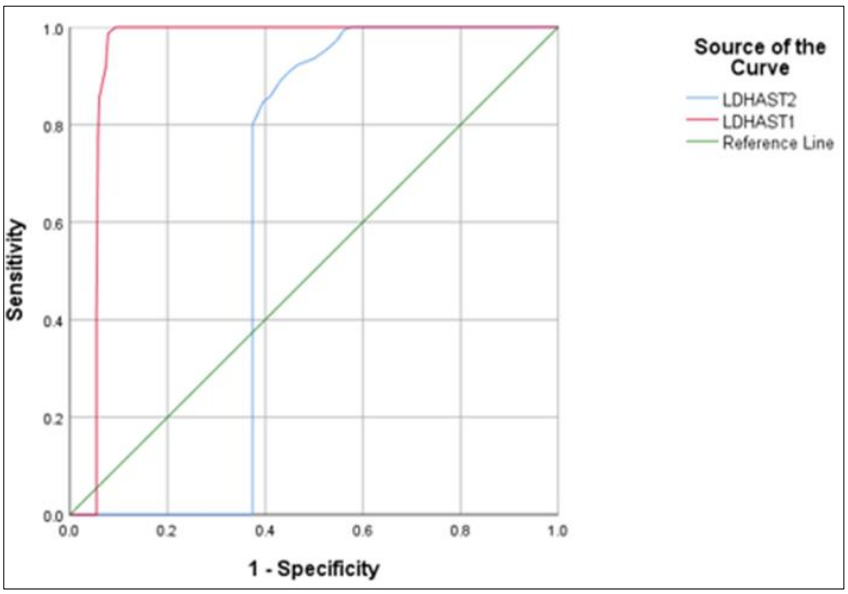

Figure 1 The area under the receiver operating characteristic analysis

*LDH: AST: 1: Admission lactate dehydrogenase to aspartate aminotransferase ratio; *LDH: AST 1: Lactate dehydrogenase to aspartate aminotransferase ratio average during admission days.

5. Conclusion

The involvement of the liver in viral infections is directly correlated with mortality, as this correlation is very clear. Therefore, it is of the utmost importance to incorporate hepatic enzymes as a criterion when evaluating patients who have viral infections. This is because of the impact that elevated liver enzymes have on immune cells and, as a result, the overall clinical outcomes. Since this is the case, it is essential for viral patients to undergo daily monitoring of their liver enzymes on a consistent basis. This study has some limitations because it was designed in a retrospective fashion. It is essential to carry out a more comprehensive, multi-location, and prospective research project in order to take into account the myriad of factors that have the potential to influence the outcomes. Our findings, despite the fact that they are subject to certain limitations, have the potential to add significance to the existing pieces of evidence that are subject to rapid change and debate. To take into account the many different aspects that could potentially have an effect on the outcomes, it is essential to carry out an investigation that is more comprehensive, multi-sited, and focused on the future. Despite the fact that there are some restrictions, our findings might be able to offer some insightful contributions to the ongoing discussion concerning the evidence that is constantly shifting and being contested.

Compliance with ethical standards

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Disclosure of conflict of interest

There is no conflict of interest in this manuscript

Statement of informed consent

Owing to the retrospective design of this study, the informed consent form was waived.

References

[1] World Health Organization. Coronavirus disease (COVID-2019) situation reports. https ://www.who.int/emergencies/diseases/novel -coronavirus-2019/ situation-reports/. Accessed 25 may 2022.

[2] S Wong SH, Lui RNS, Sung JJY.. VIRAL and the digestive system. J Gastroenterol Hepatol 2020;35:744–8 .

[3] . Cui, J., Li, F. & Shi, Z. L. Origin and evolution of pathogenic coronaviruses. Nat. Rev. Microbiol. 17, 181–192.

[4] Feng, Y. & Gao, G. F. Towards our understanding of SARS-CoV, an emerging and devastating but quickly conquered virus. Comp Immunol. Microbiol. Infect. Dis. 30, 309–327.

[5] Hui, D. S. et al. Middle East respiratory syndrome coronavirus: risk factors and determinants of primary, household, and nosocomial transmission. Lancet Infect. Dis. 18, e217–e227.

[6] Mahase, E. Viral: WHO declares pandemic because of “alarming levels” of spread, severity, and inaction. BMJ 368, m1036.

[7] Lu, R. et al. Genomic characterisation and epidemiology of 2019 novel coronavirus: implications for virus origins and receptor binding. Lancet 395, 565–574.

[8] Hoffmann, M. et al. SARS-CoV-2 cell entry depends on ACE2 and TMPRSS2 and is blocked by a clinically proven protease inhibitor. Cell .2020.02.052 (2020).

[9] Huang, C. et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet 395, 497–506.

[10] Guan, W. J. et al. Clinical Characteristics of Coronavirus Disease 2019 in China. N. Engl. J. Med. 2002 032 (2020).

[11] Young, B. E. et al. Epidemiologic Features and Clinical Course of Patients Infected With SARS-CoV-2 in Singapore. JAMA.2020.3204 (2020).

[12] Arentz, M. et al. Characteristics and Outcomes of 21 Critically Ill Patients With VIRAL in Washington State. JAMA.2020.4326 (2020).

[13] Zhou, Z. et al. Effect of gastrointestinal symptoms on patients infected with VIRAL. Gastroenterology .2020.03.020 (2020).

[14] Chai, X. et al. Specific ACE2 expression in cholangiocytes may cause liver damage after 2019-nCoV infection. J, bioRxiv .02.03.93176 6 (2020).

[15] Liang, W. et al. Diarrhoea may be underestimated: a missing link in 2019 novel coronavirus. Gut -2020-32083 2 (2020).

[16] Zhang, H. et al. The digestive system is a potential route of 2019-nCov infection: a bioinformatics analysis based on single-cell transcriptomes. J. bioRxiv.30.92780 6 (2020).

[17] Zhou, F. et al. Clinical course and risk factors for mortality of adult inpatients with VIRAL in Wuhan, China: a retrospective cohort study. Lancet 395, 1054–1062. -6736(20)30566 -3 (2020).

[18] Strnad, P., Tacke, F., Koch, A. & Trautwein, C. Liver - guardian, modifier and target of sepsis. Nat. Rev. Gastroenterol. Hepatol. 14, 55–66. 2016.168 (2017).

[19] Zhang, C., Shi, L. & Wang, F. S. Liver injury in VIRAL: management and challenges. Lancet Gastroenterol. Hepatol. 5, 428–430. 1253(20)30057 -1 (2020).

[20] Kumar, M. P. et al. Coronavirus disease (VIRAL) and the liver: a comprehensive systematic review and meta-analysis. Hepatol. Int. 2-020-10071 -9 (2020).

[21] Giannini, E. G., Testa, R. & Savarino, V. Liver enzyme alteration: a guide for clinicians. CMAJ 172, 367–379. 10407 52 (2005).

[22] Jung, K., Pergande, M., Rej, R., Schreiber, G. & Schimmelpfennig, W. Mitochondrial enzymes in human serum: comparative determinations of glutamate dehydrogenase and mitochondrial aspartate aminotransferase in healthy persons and patients with chronic liver diseases. Clin. Chem. 31, 239–243 (1985).